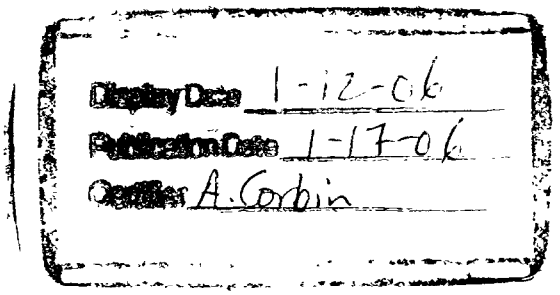
DEPARTMENT OF HEALTH AND HUMAN SERVICES



DDM

Food and Drug Administration

21 CFR Part 210

[Docket No. 2005N–0285]

Current Good Manufacturing Practice Regulation and Investigational New Drugs; Companion Document to Direct Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is publishing this companion proposed rule to the direct final rule, published elsewhere in this issue of the **Federal Register**, which is intended to amend our current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational "Phase 1" drugs from complying with the regulatory requirements. We will instead exercise oversight of production of these drugs under the agency's general statutory CGMP authority and investigational new drug application (IND) authority. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a draft guidance for industry entitled "INDs—Approaches to Complying With CGMP During Phase 1" to provide further guidance on the subject.

DATES: Submit written or electronic comments by [*insert date 75 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061,

NPR 1

Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/comments*.

FOR FURTHER INFORMATION CONTACT: Monica Caphart, Center for Drug Evaluation and Research (HFD–320), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–9047; or Christopher Joneckis, Center for Biologics Evaluation and Research (HFM–1), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–435–5681.

SUPPLEMENTARY INFORMATION:

I. Background

As described more fully in the related direct final rule, a Phase 1 clinical trial includes the initial introduction of an investigational new drug into humans. Such studies are aimed at establishing basic safety and are designed to determine the metabolism and pharmacologic actions of the drug in humans. The total number of subjects in a Phase 1 study is limited—generally no more than 80 subjects. This is in contrast to Phase 2 and Phase 3 trials, which may involve substantially greater numbers of subjects, exposing more subjects to the drug product, and which aim to test the effectiveness of the drug product.

For several reasons, we believe that production of human drug products, including biological drug products, intended for use in Phase 1 clinical trials should be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211 (21 CFR parts 210 and 211). First, even if exempted from the requirements of our CGMP regulations in parts 210 and 211, investigational drugs remain subject to the statutory provisions that deem a drug adulterated for failure to comply with CGMPs (21 U.S.C. 351(a)(2)(B)).

Second, we oversee drugs for use in Phase 1 trials through our existing IND authority. Every IND must contain, among other things, a section on

chemistry, manufacturing, and control information that describes the composition, manufacture, and control of the investigational drug product (21 CFR 312.23(a)(7)). This information should suffice to enable us to adequately protect subjects in early Phase 1 trials.

II. Additional Information

This proposed rule is a companion to the direct final rule published in the final rules section of this issue of the **Federal Register**. The proposed rule and the direct final rule are identical. This companion proposed rule provides the procedural framework to proceed with standard notice-and-comment rulemaking if the direct final rule receives significant adverse comment and is withdrawn. The comment period for the companion proposed rule runs concurrently with the comment period of the direct final rule. Any comments received on this companion proposed rule will also be treated as comments on the direct final rule and vice versa.

For additional information, see the corresponding direct final rule published in the final rules section of this issue of the **Federal Register**. All persons who may wish to comment should review the rationale for these amendments set out in the preamble discussion of the direct final rule. A significant adverse comment is one that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. A comment recommending a rule change in addition to this rule will not be considered a significant adverse comment, unless the comment states why this rule would be ineffective without the additional change. If no significant adverse comment is received in response to the direct final rule, no further action will be taken related to this companion proposed rule. Instead, we will

publish a confirmation notice within 30 days after the comment period ends, and we intend the direct final rule to become effective 30 days after publication of the confirmation notice. If we receive significant adverse comments, we will withdraw the direct final rule. We will proceed to respond to all of the comments received regarding the direct final rule, treating those comments as comments to this proposed rule. The agency will address the comments in a subsequent final rule. We will not provide additional opportunity for comment.

III. Legal Authority

Under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 201 *et seq.*) a drug is deemed adulterated if the methods used in, or the facilities, or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated in conformity with CGMPs to ensure that such drug meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. The rulemaking authority conferred on FDA by Congress under the act permits the agency to amend its regulations as contemplated by this direct final rule. Section 701(a) of the act (21 U.S.C. 371) gives FDA general rulemaking authority to issue regulations for the efficient enforcement of the act. We refer readers to the legal authority section of the preamble of the 1978 CGMP regulations for a fuller discussion (43 FR 45014 at 45020–45026, September 29, 1978).

IV. Environmental Impact

The agency has determined that under 21 CFR 25.30(h) this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. The agency has considered the effect that this rule would have on small entities. Because exempting production of drugs for use in Phase 1 studies from compliance with specific regulatory requirements does not add any burden, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $115 million using the most current (2003) Implicit

Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

For a further discussion of the impacts of this rulemaking, see the Analysis of Impacts section in the corresponding direct final rule published in the final rules section of this issue of the **Federal Register**.

VI. Paperwork Reduction Act of 1995

This proposed rule contains no new information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Under the proposed rule, the production of human drug products, including biological drug products, intended for use in Phase 1 clinical trials would be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211. Parts 210 and 211 contain information collection requirements that have been approved by OMB under control number 0910–0139. As explained in the following paragraph, the information collection requirements in parts 210 and 211 would be reduced under this proposed rule.

The OMB-approved hourly burden to comply with the information collection requirements in parts 210 and 211 (control number 0910–0139) is 848,625 hours. FDA estimates that, under the proposed rule, approximately 7,315 drugs would be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211. Based on this number and the total number of drugs that are subject to parts 210 and 211, FDA estimates that the burden hours approved under control number 0910–0139 would be reduced by approximately 50,493 hours. Thus, as a result of the proposed rule,

the amended burden hours in control number 0910–0139 would be approximately 798,132 hours.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required. We invite comments on the federalism implications of this proposed rule.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. This comment period runs concurrently with the comment period for the direct final rule; any comments received will be considered as comments regarding the direct final rule. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 210

Drugs, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs it is proposed that 21 CFR part 210 be amended as follows:

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

1. The authority citation for 21 CFR part 210 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

2. Section 210.2 is revised by adding paragraph (c) to read as follows:

§ 210.2 Applicability of current good manufacturing practice regulations.

* * * * *

(c) An investigational drug for use in a Phase 1 study, as defined in § 312.21(a) of this chapter, is subject to the statutory requirements set forth at 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a Phase 1 study once the investigational drug has been made available for use by or for the sponsor in a Phase 2 or Phase 3 study, as defined in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a Phase 2 or 3 study or the drug has been lawfully marketed, the drug for use in the Phase 1 study must comply with part 211 of this chapter.

Dated: 1/9/06

January 9, 2006.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 05–????? Filed ??–??–05; 8:45 am]

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